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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,657	05/29/2001	Peter Robert Bernstein	133087.01701(Z70402-1PUS)	4679

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EXAMINER	
DESAI, RITA J	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
12/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,657	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 12-17* is/are pending in the application.

4a) Of the above claim(s) *2, 7, 13, 15, 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,12,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants election of Group III has been noted.

Claims 1, 3-6, 13, and 16 drawn to compounds and pharmaceuticals of formula as given in claim 1 wherein R1 is the piperidine group, R2 is a H.

Claims 2, 7, 12, 14, 15 and 17 are drawn to non elected.

Claims 8-11 are cancelled.

The traversal is that the examiner has not shown that it is a burdensome search nor that it is independent and distinct.

These are not the criteria for a 371 applications .

The examiner has shown a lack of unity and lack of technical feature as the core was not novel and it gave numerous iterations. The core is not a contribution over the prior art. Hence there is a lack of unity.

The lack of Unity has been made FINAL.

The claims that read on the elected group are 1, 3-6 , 13 and 16.

Claim Objections

Claim 14 is objected to because of the following informalities: Claim 14 is dependent from a canceled claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

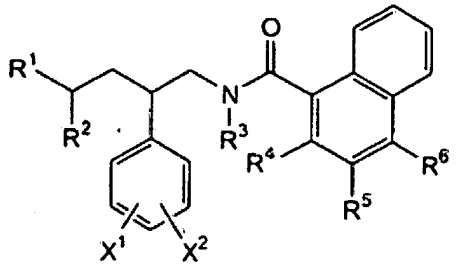
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

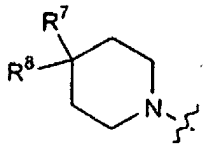
Claims 1, 3-6, 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 474561 (US equivalents , 5350852, 5236921).

In view of EP 0630887.

Applicants claims are drawn to compounds of the formula



wherein R1 is

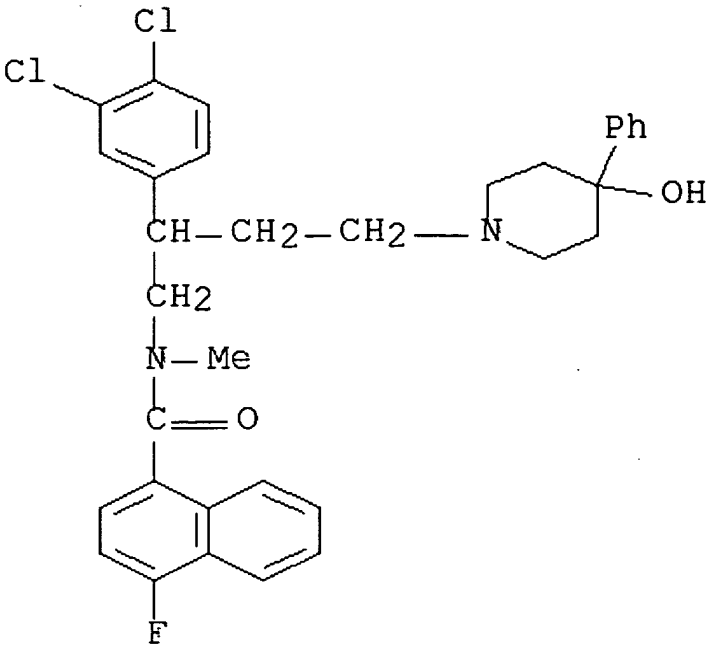


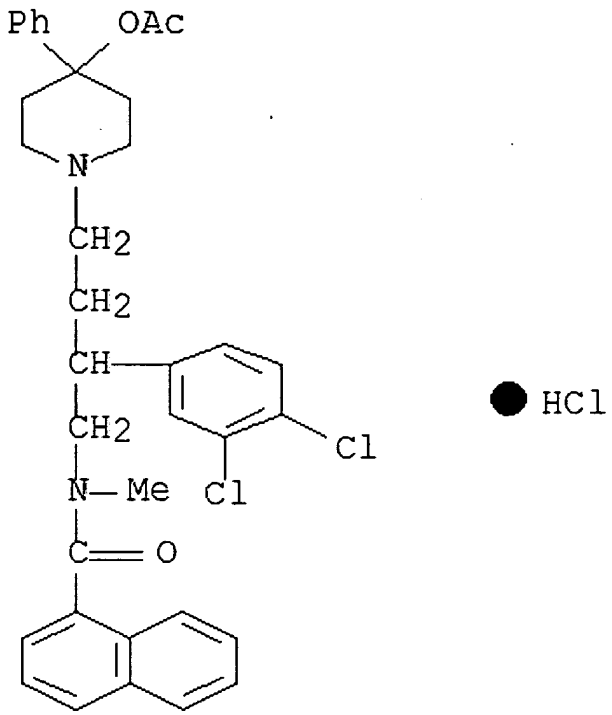
and R2 is a H , R7 is a substituted phenyl.

These compounds are tachykinin receptor antogonists also known as neurokinin 1 and 2 receptor agonists.

Scope and Content of the prior art

The prior art US 5350852 teaches similar compounds such as for example





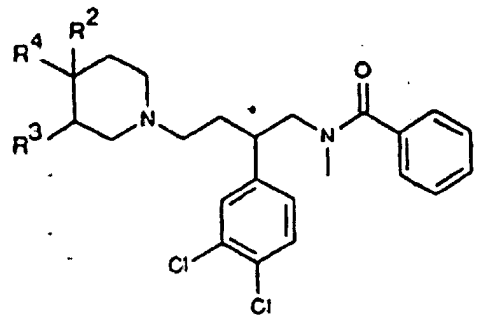
● HCl

EP 0630867 teaches similar compounds with a phenyl instead of the naphthyl group.

The substitutent on the phenyl, corresponding to the R7 position of the applicants compounds .

see claim 9 or 10 page 37, which clearly teaches the methylsulphynyl group on the phenyl on the p-position of the piperidine.

9. A compound of formula I



I

wherein R^2 and R^3 are each hydrogen and R^4 is phenyl which bears a methylthio or methylsulfinyl substituent, or a pharmaceutically acceptable salt thereof.

10. A compound as claimed in Claim 9 in which the substituted piperidino moiety of the compound of formula I is selected from 4-(4-methylthiophenyl)piperidino, 4-(2-methylsulfinylphenyl)-piperidino, and 4-(4-methylsulfinylphenyl)piperidino.

Difference between Prior Art and the claims MPEP 2141.02

The difference between the US ' 852 prior art compounds and those of the invention is that the R7 phenyl in the applicants claim is substituted.

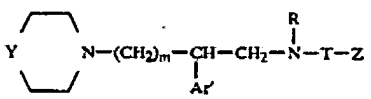
The difference between the EP '887 compounds and those of the invention is the naphthyl instead of phenyl group.

US' 852 teaches various other options for the naphthyl group , one of them is the phenyl .

Prima Facie Obviousness , Rational and Motivation MPEP 2142-2413

Both the prior art compounds have the exact same utility.

The core of the compound in US '852 is the same as that of the applicants. In column 2 of the reference there is a clear teaching that the phenyl can be substituted or not substituted.



(I)

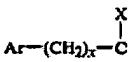
in which:

Y represents—either a group Cy—N in which

Cy represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

hydrogen, a halogen atom, a hydroxyl, a C_1-C_4 alkoxy, a C_1–C_4 alkyl, a trifluoromethyl, the said substituents being identical or different; a C_3–C_7 cycloalkyl group; a pyrimidinyl group or a pyridyl group;

or a group



in which

Ar represents a phenyl, unsubstituted or substituted one or more times with one of the substituents selected from:

hydrogen, a halogen atom, a hydroxyl, a C_1–C_4 alkoxy, a trifluoromethyl, a C_1–C_4 alkyl, the said substituents being identical or different; a pyridyl group; a thienyl group;

x is zero or one;

X represents a hydroxyl, a C_1–C_4 alkoxy; a hydroxyalkyl in which the alkyl is a C_1–C_3 group; a C_1–C_4 acyloxy; a phenacyloxy; a carboxyl; a C_1–C_4 carbalkoxy; a cyano; an aminoalkylene in which the alkylene is a C_1–C_3 group; a group —N—$(X_1)_2$ in which the groups X_1 independently represent hydrogen, a C_1–C_4 alkyl; a group

Table 3 column 22 of the '852 reference teaches the phenyl to be substituted by R1 and R1'.

Table 4 and 6 teach the naphthalene and also the phenyl on the piperidine to be substituted.

Table A column 45 teaches the equivalence of the phenyl and the naphthyl groups.

The EP' 887 teaches the substitutent on the phenyl

The activity of the compound is thus not dependent upon the substitutent on the phenyl.

This can motivate a person of skill in the art to make more compounds with different substitutents on the R7 phenyl ring with the naphthalene core and hence it is prima-facie obvious to one of skill in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 13 and 16 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R4-R6 to be H, alkyl, alkoxy or cyano, and X1 and X2 to be a halogen , hydrogen, does not reasonably provide enablement for all the other various substitutents such as

R^4 is independently selected from hydroxy, halo, C_{1-6}alkoxy, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy-carbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoylamino and aminosulfonyl;

R^5 is independently selected from hydroxy, cyano, nitro, trifluoromethoxy, trifluoromethyl, C_{1-6}alkylsulfonyl, halo, C_{1-6}alkoxy, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy-carbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoylamino, aminosulfonyl, and substituted C_{1-6}alkyl; or

R^4 and R^5 together form $-OCH_2O-$ or $-OC(CH_3)_2O-$;

R^6 is selected from hydrogen, hydroxy, cyano, nitro, trifluoromethoxy, trifluoromethyl, C_{1-6}alkylsulfonyl, halo, C_{1-6}alkoxy, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy-carbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoylamino, aminosulfonyl, and substituted C_{1-6}alkyl

The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims: The instant claims encompass many compounds with a core and different groups hanging off of it.

2) The nature of the invention: The invention is a chemical compound used as a pharmaceutical.

3) The state of the prior art: The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Also the state of the prior art is that it involves screening in vitro and invivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of diseases as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Also according to Side reaction as given below , very difficult to synthesis and with different functional groups it is not predictable what the product of compounds with a similar stating material would yeild.
How to make :-

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they wereto learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ....." Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Thus it is not very easy to synthesis compounds.

4) The level of one of ordinary skill: The ordinary artisan is highly skilled.

5) The level of predictability in the art:
How to use:- It is noted that the pharmaceutical art is unpredictable , requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. The level of unpredictability is in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

How to make :-

Thus it is not very easy to synthesis compounds.

6) The amount of direction provided by the inventor: The inventor provides very little direction in the instant specification. Page 74 and 75 gives some examples of compounds made. These do not correspond to the scope of the compounds claimed.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here. As per MPEP 2164.01 (b):
A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991,169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

There are no starting material provided with respect to the various R4-R6 and X1 and X2 substitutents.

7) The existence of working examples: The instant specification does not have any working examples with respect to the various substitutents as given above

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of all the above factors, guidance and state of the art , it would require an undue amount of experimentation to make the invention of the claims with various substitutents , or for using them to treat diseases or have neurokinin activity.

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention. The examiner has shown the state of the art and predictability in the art and in view of the guidance and examples provided it is clear that the full scope of the compounds as written is not enabled.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention , not for vague intimations of general ideas that may or may not be workable."

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that,

> based on the evidence regarding each of the above factors, the specification, at the time the application was flied, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Conclusion

Claims 1, 3-6, 13 and 16 stand rejected.

Claims 2, 7, 12, 14, 15 and 17 are withdrawn as being non-elected.

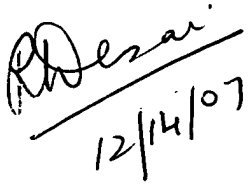
Claims 8-11 are cancelled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625



R.D.
December 14, 2007